C2

56. (Amended) A method for preparing a product for the treatment of diabetes mellitus or hypoglycemia, which method comprises bringing an effective amount of an [a] amylin agonist [compound having amylin-like activity] into the form of a composition suitable for therapeutic administration.

C3

66. (Amended) A pharmaceutical composition for use in the treatment of diabetes mellitus or hypoglycemia which comprises a therapeutically effective amount of a peptide agonist of amylin [having amylin like activity], said composition being lyophilized.

67. (Amended) A pharmaceutical composition for use in the treatment of diabetes mellitus or hypoglycemia which comprises a therapeutically effective amount of a peptide agonist of amylin [having amylin-like activity], said composition being disposed in a vehicle suitable for delayed-release administration of said peptide.

C4

72. (Amended) A pharmaceutical composition for use in the treatment of diabetes mellitus or hypoglycemia which comprises a suspension of a peptide agonist of amylin [having amylin-like activity], said suspension being formulated with a zinc salt in a pharmaceutically acceptable buffer, said suspension being suitable for parenteral administration.

Please add the following claims:

C5

76. The composition of claim 46 which further comprises an effective amount of insulin.

77. The composition of claim 47 which further comprises an effective amount of insulin.

78. The method of claim 56 which further comprises bringing an effective amount of insulin together with said amylin agonist to form said composition.

79. The method of claim 58 which further comprises bringing an effective amount of insulin together with amylin to form said composition.

80. The pharmaceutical composition of claim 66 which further comprises a therapeutically effective amount of insulin.

81. The pharmaceutical composition of claim 67 which further comprises a therapeutically effective amount of insulin.

82. The pharmaceutical composition of claim 72 which further comprises a therapeutically effective amount of insulin.

REMARKS

Claims 2-4, 6-18, 20-21, 23, 29-31, 34-40 have been cancelled without prejudice to their inclusion in a continuing application in view of the fact that the restriction requirement of Paper No. 6 was made final in Paper No. 9 in the parent case. It appears that claims 43-45 were inadvertently omitted from the listing of withdrawn claims at page 2 of the December 10, 1990 Office Action. These claims 43-45 are listed on the cover page and in the March 16, 1990 Office Action as standing withdrawn and, accordingly, Applicant has cancelled these claims as well.

Claims 46, 56, 66, 67 and 72 have been amended in order to more particularly point out and to reflect the fact that agonists of amylin such as those disclosed in the specification (CGRP, for example), are included within the scope of Applicant's invention as therein described.

1. Section 101

Claims 46-75 stand rejected under 35 U.S.C. §101 on the assertion that Applicant's invention is "inoperative and therefore lacks utility" (December 10, 1990 Office Action at page 2). The PTO further stated that, "[s]ince the alleged utility is unbelievable upon its face, applicant must have supportive data (in vivo experimental or clinical data) to overcome the [§101] rejection" (December 10, 1990 Office Action at page 2). While Applicant has argued that his invention is not such as to necessitate the provision of further data, in order to expedite

prosecution of this case Applicant supplies herewith in vivo experimental results with regard to (1) the use of amylin in the treatment of hypoglycemia, and (2) the use of amylin in conjunction with insulin therapy in the treatment of diabetes.

Amylin therapy: The Young Declaration submitted herewith describes experiments which establish that amylin is an effective hyperglycemic agent. That is, amylin can be used to treat hypoglycemia and aid in normalizing blood glucose levels (Young Declaration ¶ 3-6). The results set forth in the Young Declaration clearly demonstrate the operativeness of amylin for use in the treatment of hypoglycemia in standard test animals (Young Declaration ¶ 6), and those skilled in the art will recognize that such experiments are predictive of utility in the treatment of hypoglycemia in humans (Young Declaration ¶ 6).

Amylin/Insulin Therapy: The Young Declaration also describes experiments utilizing a standard animal model for diabetes, the streptozotocin-diabetic rat, in which the effects of treatment of diabetes with insulin alone and with insulin plus amylin were examined and compared (Young Declaration ¶ 7). The treatment of diabetic test animals with amylin and insulin not only showed utility, but displayed a greater utility than therapy with insulin alone (Young Declaration ¶ 9).

Streptozotocin is a relatively specific beta cell toxin which, when introduced into a test animal in multiple small doses, will produce nearly complete beta cell destruction and severe diabetes. Once these animals become diabetic they can be maintained by treatment with once-daily injections of insulin. Streptozotocin-diabetic rats, however, as well as other animal models of insulin-dependent diabetes, have a marked depletion of liver glycogen which is only partially corrected with insulin. This characteristic of diabetes is important, in part because the liver is the main organ which secretes glucose into the blood,

which it does in response to catecholamines (e.g., adrenaline), and in response to the insulin counterregulatory hormone glucagon, which are designed to result in raised blood glucose levels. Liver glycogen is the predominant source of this glucose.

Full restoration of liver glycogen can thus be expected to provide extra protection against hypoglycemia in diabetics, because liver glycogen serves as the immediate source for blood glucose when the body needs sugar quickly. The experiments set forth in the Young Declaration showed that diabetic test animals which received no therapy showed a 67% decrease in liver glycogen concentration compared to normal rats (Young Declaration ¶ 8). Diabetic test animals receiving insulin replacement still had a 35% decrease in liver glycogen compared to normal rats (Young Declaration ¶ 8). In insulin-treated diabetic test animals supplemented with daily amylin, on the other hand, there was a dose-dependent increase in liver glycogen concentration above that in rats treated with insulin alone (Young Declaration ¶ 8). The experiments described in the Young Declaration show not only that combined replacement of amylin and insulin is useful, but that it can restore normal levels of liver glycogen (Young Declaration ¶¶ 8-9). They also show that this glycogen restoration achieved by combined replacement of amylin and insulin is not achieved by insulin alone (Young Declaration ¶¶ 8-9). The Young Declaration confirms the operativeness of amylin for use in the treatment of diabetic animals (Young Declaration ¶ 10), and those skilled in the art will recognize that such experiments are predictive of utility in the treatment of diabetes mellitus in humans (Young Declaration ¶ 10).

Having provided the in vivo data requested by the Examiner further confirming the utility of the claimed inventions, Applicant respectfully requests the §101 rejection of claims 46-75 be withdrawn.

2. Section 112, First Paragraph

The PTO has objected to the specification and has rejected claims 46-75 under 35 U.S.C. §112, first paragraph (December 10, 1990 Office Action at page 2). The Examiner stated that applicant has not enabled one skilled in the art to use the compositions effectively in the treatment of diabetes mellitus or hypoglycemia for the following reason:

> Since it is well known in the art that the effective treatment of diabetes by pharmaceutical compositions has only been accomplished by the use of insulin, the allegation that a new composition is as effective is unbelievable upon its face.

(December 10, 1990 Office Action at page 3). It is settled that, "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." In re Chilowsky, 108 U.S.P.Q. 321, 325 (CCPA 1956). In any event, and as discussed above, the Young Declaration provides experimental results on utility sought by the Examiner and Applicant asks that this §112 rejection of claims 46-75 be withdrawn as well.

The Examiner also objected to applicant's arguments regarding the coadministration of amylin and insulin together on the ground that, because applicant's claimed compositions do not include insulin, such arguments are "not pertinent as to the effectiveness of amylin alone" (December 10, 1990 Office Action at pages 4-5). The transitional phrase "comprising" used in Applicant's claims has an interpretation equivalent to the word "including," that is, the claimed invention will include all of the elements set forth in the body of the claim, but may contain in addition thereto an unlimited number of unrecited elements. Thus, even though certain claims do not reference insulin, they are broad enough to include the administration of amylin and insulin, as set forth in the specification. Moreover, the co-administration of amylin and insulin may be accomplished without the amylin and insulin being combined in the same composition.

For example, the two compositions could be administered separately as described in the specification, for example, at page 5. See also Young Declaration. Applicant has also added new dependent claims 76-82 which expressly recite this amylin/insulin formulation.

The Examiner further indicated that because Applicant's "claimed compositions can have many different compounds in place of amylin" that Applicant's disclosure "has not shown that any of [these] compound[s] in a pharmaceutical composition are effective" (December 10, 1990 Office Action at page 5). Applicant has amended claims 4, 56, 66, 67, and 72 to reflect the fact that agonists of amylin as disclosed in the specification (such as CGRP) are also contemplated by his invention, and in order to adequately protect that invention. Further support is provided by the Young Declaration, which confirms that agonists of amylin will also be useful both in the treatment of hypoglycemia and in conjunction with insulin therapy (Young Declaration ¶ 11).

It is also important to keep in mind current law which instructs that Applicant's specification need not disclose each and every possible amylin agonist to render it enabling. See, e.g., In re Angstadt, 190 U.S.P.Q. 214 (CCPA 1976). There are sound and well-established reasons for this, some of which were described by the Angstadt court as follows:

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to

> discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

190 U.S.P.Q. at 218. Thus, as a matter of law, Applicant is not required to test every species of amylin agonist encompassed by his claims.

Furthermore, it cannot be disputed that Applicant's work is pioneering in nature; it is "of such novelty and importance as to mark a distinct step in the progress of the art, as distinguished from a mere improvement or perfection of what had gone before." Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 562 (1898). Having invented broadly, Applicant is entitled to like claim coverage. Applicant's invention did not arise merely from what went before, for example, from tinkering with insulin or various methods of making it. It arose out of Applicant's breakthrough discoveries including the amylin molecule and its biological characteristics and significance, all of which went undetected even after decades of intensive worldwide research in the field of diabetes. Applicant's work culminated in his determination that combined treatment with insulin and an agonist of amylin (such as amylin itself), even though the two entities appeared to have opposing glucose-modulating properties, would revolutionize treatment for a large patient population that included the world's diabetics. He was right, and his invention represents a medical innovation of historic proportions.

Our patent laws are designed to reward such determination and insight, and it has long been required that an invention which carries the art a substantial step forward be given broad protection. Many years ago, for example, the great jurist Learned Hand, in Patent Royalties Corp. v. Land O'Lakes

Creameries, Inc., 89 F.2d 624, 628 (2d Cir. 1937), characterized this requirement as follows:

> The patent was a long advance; it gave to the trade a new protection it had sought for many years; the inventors' protection ought to be correspondingly liberal.

Because of the extraordinary contribution a pioneer invention makes to the progress of the useful arts, it is given extraordinary protection. In Grubman Engineering and Mfg. Co. v. Goldberger, 47 F.2d 151, 153 (2d Cir. 1931), it was said, also by Judge Learned Hand:

> The latitude we give does indeed depend upon how far the inventor has stepped forward; he may be a "pioneer." When he is, we stretch his claims to the breaking point.

While Judge Hand's comment there sprang from patent litigation proceedings, the philosophy is unerringly applied in the instant case. In light of Applicant's pioneering invention -- which stands against a background devoid of any significant prior art -- and in view of the Young Declaration which confirms the utility of amylin and amylin agonists in that invention (Young Declaration ¶ 11), Applicant respectfully requests that the PTO's § 112 rejection be withdrawn.

3. Section 103

The Examiner has rejected claims 56-65 under 35 U.S.C. §103 as being "unpatentable over pages 10-11 of applicants' specification." The rejection is based on In re Durden, 226 U.S.P.Q. 359 (Fed. Cir. 1985). The PTO states: "Applicant's specification teach[es] that the claimed compositions are prepared by the conventional methods well known in the art" (December 10, 1990 Office Action at page 5).

Claims 56-65 cover methods for preparing therapeutic products. The broadest claim, claim 56, as amended, reads as follows:

> 56. A method for preparing a product for the treatment of diabetes mellitus or hypoglycemia, which method comprises bringing

an effective amount of an amylin agonist into the form of a composition suitable for therapeutic administration.

At pages 10-11 the Specification describes methods for the therapeutic preparation of amylin. Nevertheless, under any reading of the Durden case, the claimed methods are not obvious within the meaning of §103.

The Federal Circuit took great care to emphasize in In re Durden that each obviousness case must be decided on the basis of its own particular facts (226 U.S.P.Q. at 361), and that the test is whether the claimed method as a whole is obvious (226 U.S.P.Q. at 362). Accordingly, the fact that Applicant's claimed compositions might be prepared utilizing certain formulation methods available in the art is not in itself determinative of obviousness.

In order to sustain the §103 objection, the PTO must establish a threshold case of obviousness, i.e., that the prior art suggests the claimed invention to those of ordinary skill in the art; that it provides the motivation to make the proposed invention. It has been held that the motivation to make a specific invention is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the item to have, if made. In re Newell, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir. 1989). Thus, the critical inquiry is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. Id.

Here, however, the PTO has quite forcefully indicated that there would be no motivation to make the claimed compositions because they would not be expected to be of any use. Indeed, the PTO previously asserted that the claimed utilities are "unbelievable on their face." Applicant has clearly supported his claims of utility (see, e.g., the Young Declaration), but it cannot now be said in hindsight with knowledge of such evidence

that the preparation of the claimed compositions would have been obvious. There can be no motivation to make something that one firmly believes will not work and will, thus, be of no value.

In light of the earlier view of inoperability, in fact, Applicant's evidence in support of utility can be likened to evidence of "unexpected results", evidence which has long been held to be compelling in reaching a conclusion of nonobviousness. An insight which is contrary to the understanding and expectations of the art points unerringly to patentability. E.g. Schenck, A.G. v. Nortron Corp., 218 U.S.P.Q. 698, 700 (Fed. Cir. 1983).

In summary, it is submitted that the methods of the claims in question would not have been obvious in view of the generally known methods of preparing compounds for therapeutic administration which are discussed at pages 10-11 of the specification, and Applicant asks that the §103 rejection of claims 56-65 be withdrawn.

4. Section 112, Second Paragraph

The PTO has rejected claims 46-75 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner has objected to the terms "compound having amylin-like activity," "peptide," "functional amylin peptide fragment," "conservative variant of amylin," "CGRP peptide fragment," and "conservative variant of CGRP" as being "indefinite as to the scope of the compounds included in the claims.

As stated in the Manual of Patent Examining Procedure, all that is required to satisfy the claim definiteness requirement is definition "with a reasonable degree of particularity and distinctness."

> When the examiner is satisfied that patentable novelty is disclosed and it is

> apparent to the examiner that the claims are directed to such patentable subject matter, he should allow claims which define the patentable novelty with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.

(MPEP §706.03(d) (5th ed. 1983) (emphasis in original). See also Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986):

> "[I]f the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," ....

In this instance, Applicant submits that those skilled in the art would know what is meant by the terms objected to by the Examiner. The term "compound having amylin-like activity" is self-explanatory. The activity of amylin is described throughout the specification. For example, at page 7, line 27 to page 8, line 3, amylin's effects are described as "modulating and reducing the hypoglycemic effects of insulin, both by reducing the release of insulin in relation to a given glucose stimulus, and (more importantly in the case of type 1 diabetes) by reducing the rate of storage of glucose as glycogen." Because Applicant made the broad, pioneering discovery that both amylin and agonists of amylin such as CGRP have glucose-raising properties useful for certain therapeutic treatments, Applicant is entitled to claim broadly. There is no imprecision in claim terminology, and those in the art will comprehend the scope of the claims to which the PTO objected. However, in order to remove any doubt that may remain as to the definition of the claimed invention, Applicant has amended the claims to recite amylin "agonists" in place of the phrase "compound having amylin-like activity." The term agonist captures Applicant's invention as described in the specification and is well understood in the art. See Young Declaration ¶ 11.

Applicant also submits that those skilled in the art would know the meaning of the term "peptide." The other terms objected to by the Examiner are described in the specification. For example, the term "functional peptide fragment" is discussed at page 5, lines 2-5:

> A functional fragment of amylin or deamidated amylin or CGRP is meant to include a peptide fragment at least 5 amino acid residues in length, which performs in vivo a therapeutic function of the complete amylin or deamidated amylin or CGRP peptide.

For example, the term "conservative variant" is discussed at page 5, lines 5-12:

> A conservative variant is meant [] to include [sic, a] peptide which is substantially, though not completely, homologous with amylin or deamidated amylin or CGRP or fragments thereof, but which is functionally equivalent thereto. (See M.O. Dayhoft, A Model of Evolutionary Change in Proteins, in Atlas of Protein Sequence and Structure," Foundation 1978, pages 345-352). See Cooper, et al., P.N.A.S. (1987) supra.

Moreover, mere breadth of a claim does not in itself cause indefiniteness. See, e.g., Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

> The phrase "so dimensioned" is as accurate as the subject matter permits, automobiles being of various sizes. See Rosemont, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 U.S.P.Q. 1, 7 (Fed. Cir. 1984). As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, §112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces and hundreds of different automobiles be listed in the patent let alone that they be listed in the claims.

Finally, PTO rejected claims 56-65 as being "functional as to the point of novelty," the basis for the rejection being that "the process is defined as bringing an effective amount of a compound into the form of a composition suitable for therapeutic administration" (December 10, 1990 Office Action at page 6). Applicant respectfully notes that the doctrine of functionality at the point of novelty has been overruled. In re Swinehart, 169

U.S.P.Q. 225, 228-29 (CCPA 1971). Additionally, the use in claims of the functional term "an effective amount" is an established practice and has been approved in many cases. See, e.g., In re Caldwell, 138 U.S.P.Q. 243, 246-47 (CCPA 1963) (the term "effective amount" in claims to methods of stimulating animal growth by the use of aspirin was held not objectionable); In re Halleck, 164 U.S.P.Q. 647, 649 (CCPA 1970) (the term "an effective amount" in claims to compositions and methods for stimulating animal growth by the use of a "peristalsis-regulating substance" was held not objectionable).

CONCLUSION

For reasons set forth above, Applicant submits that his pending claims are in condition for allowance and seeks an early Notice thereof. Should there be any issues or questions, the Examiner is encouraged to telephone the undersigned in order that they may be promptly resolved.

Dated: 7-23-91

Respectfully submitted,

By: _____

Bradford J. Duft
Registration No. 32,219
LYON & LYON
611 W. Sixth Street
Suite 3400
Los Angeles, CA 90017
(619) 552-8400